



TITLE:

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Serum Complements as Indicator for Predicting Vasospasm and Its Severity after Aneurysmal Subarachnoid Hemorrhage

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Abstract

We investigated serum complements (CH50, C3, C4) after aneurysmal subarachnoid hemorrhage in 21 patients over a 2 to 3-week period. For a control, we performed the same examination on patients with non-subarachnoid hemorrhage such as hypertensive intracerebral hemorrhage. There were no remarkable changes of serum complements in the control patients. Preoperative grading (by *Hunt and Hess*) was well correlated with the C4 level but not the C3 level. C4 levels in patients without symptomatic vasospasm did not change markedly after subarachnoid hemorrhage over investigation. They decreased severely, however, in patients with severe vasospasm and major neurological deficits. The patients with mild symptomatic vasospasm and no major neurological deficits showed transient decreases of C4 levels 5 to 10 days after subarachnoid hemorrhage.

Our data showed that sequential measurements of serum complements C4 after subarachnoid hemorrhage was useful for choosing the method of therapy and for predicting the prognosis of aneurysmal patients after subarachnoid hemorrhage.

Introduction

Vasospasm has been a significant problem in managing patient with aneurysmal subarachnoid hemorrhage. The etiology of this arterial narrowing remains unknown and definitive treatment is not available.

Vasculopathy has been emphasized as a cause of vasospasm for many years^{8,23}. In animal experiments, as well as in clinical trials, anti-inflammatory drugs and steroid hormones have been effective in treating vasospasm to some degree. Many chemical substances derived from red blood cells, white blood cells and vessel walls have been proposed as the cause of vasculopathy. In recent years, complement activation has been stressed as initiating many diseases caused by these chemical substances^{1,3,4-6,12-15}.

Although there have been many studies monitoring biochemical substances in the blood and

Key words: Aneurysm, Immune complex, Subarachnoid hemorrhage serum complement, Vasospasm.

索引語: 脳動脈瘤, 血清補体, クモ膜下出血, 脳血管攣縮, 免疫複合体.

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Table 1 Summary of 21 cases with aneurysmal subarachnoid hemorrhage and 4 cases of control

Case No.	Age	Sex	Site of aneurysm	Grade (H&H)	Fisher group	symptomatic vasospasm	outcome	comments	
1	76	f	a-com	III	4	—	poor	ICH	
2	64	f	lt-mca	II	3	—	good		
3	39	f	rt-mca	III	3	+	good		
4	54	m	rt-ic-pc	II	3	—	good		
5	43	m	a-com	II	3	—	good	non-clip	
6	51	f	rt-mca	II	3	+	good		
7	68	m	dist-aca	IV	4	—	dead		
8	64	f	lt-ic-pc	V	3	+	dead		
9	42	f	rt-mca	IV	3	—	good		
10	47	f	a-com	II	3	+	good		
11	57	f	lt-mca	IV	4	—	good		
12	71	f	rt-va-pica	IV	3	+	dead		
13	38	m	a-com	III	3	—	good		
14	75	f	a-com	IV	3	+	poor		
15	42	m	a-com	V	4	—	dead		
16	78	f	lt-mca	IV	4	—	poor		
17	46	m	dist-aca	III	4	—	good		
18	68	f	lt-mca	IV	4	—	good		
19	52	f	a-com	II	3	—	good		
20	42	f	rt-mca	IV	3	—	good		
21	65	f	lt-mca	V	4	—	dead		
1	60	f	HICH (Thalamic hemorrhage with ventricular hematoma)						
2	52	m	HICH (Putarminal hemorrhage)						
3	63	m	HICH (Cerebellar hemorrhage with ventricular hematoma)						
4	59	m	HICH (Thalamic hemorrhage with ventricular hematoma)						

ICH: intracerebral hemorrhage, HICH: hypertensive intracerebral hemorrhage, H&H: Hunt and Hess

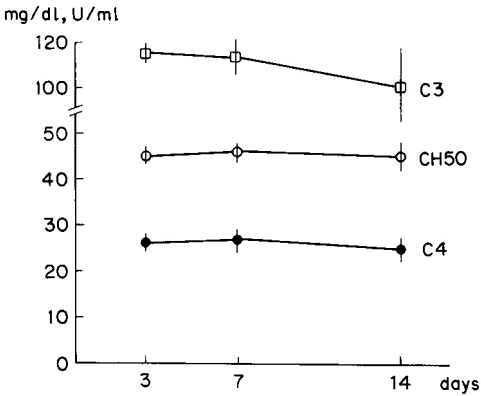


Fig. 1 Serum levels of complements (Upper: C3, Middle: CH50, Bottom: C4) in 4 control patients (mean \pm standard error of the mean). There are no statistical changes of complements after onset of the disease (by analysis of variance).

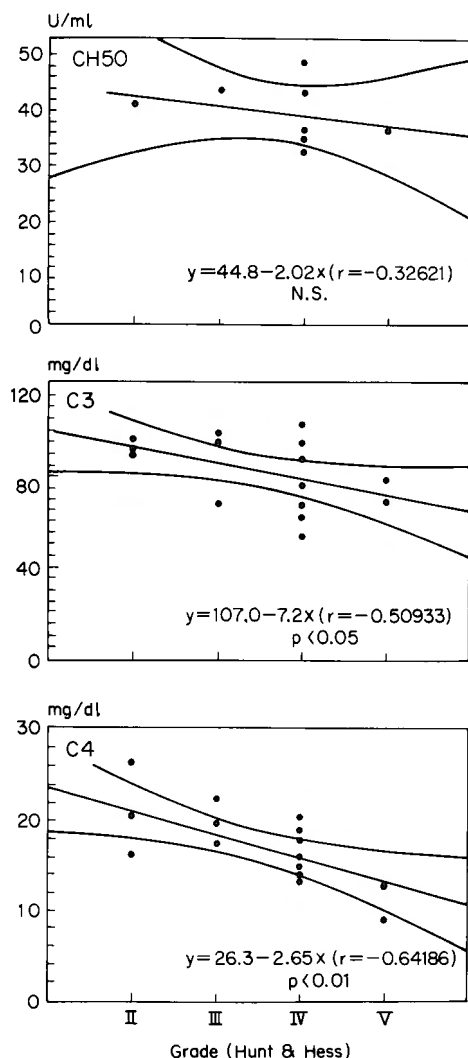


Fig. 2 Correlation of initial subarachnoid grading (Hung & Hess) and serum complements. The linear correlation coefficient (r) = -0.32621 in CH50 (Not significant), -0.50933 in C3 ($p < 0.05$) and -0.64186 in C4 ($p < 0.01$). The curved lines represent the 95% confidence intervals about each regression line.

cerebrospinal fluid, no ideal biochemical marker related to late cerebral vasospasm has yet been found^{16,19}. We now report on sequential changes of serum complements as ideal biochemical markers for predicting the occurrence and severity of late cerebral vasospasm in patients with ruptured cerebral aneurysms.

Methods

Twenty-one aneurysmal subarachnoid hemorrhage patients admitted to our department were examined in this study. Using the grading system of *Hunt and Hess*⁹. We had 6 patients in Grade

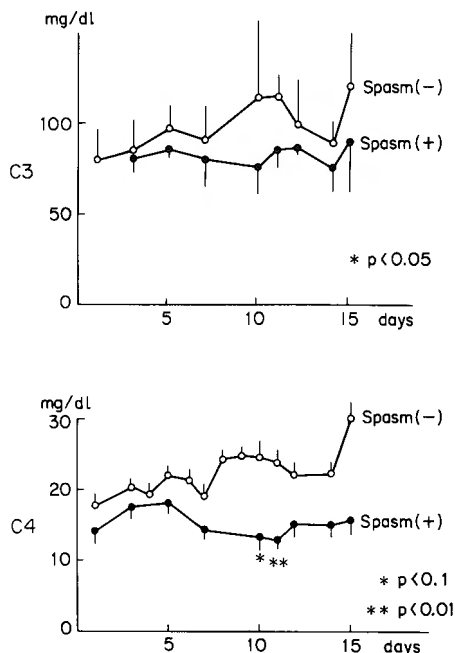


Fig. 3 Serum levels of C3 (Upper) and C4 (Lower) (mean \pm standard error of the mean) in 15 patients without symptomatic vasospasm (open circles) and in 5 patients with symptomatic vasospasm (filled circles).

Compared to C3 levels, C4 levels were much lower in patients with symptomatic vasospasm than in patients without (open circles).

C4 levels in patients with symptomatic vasospasm decreased 5 to 7 days after subarachnoid hemorrhage to mostly under 20 mg/dl, however, C4 levels in patients without symptomatic vasospasm mostly increased after subarachnoid hemorrhage to above 20 mg/dl.

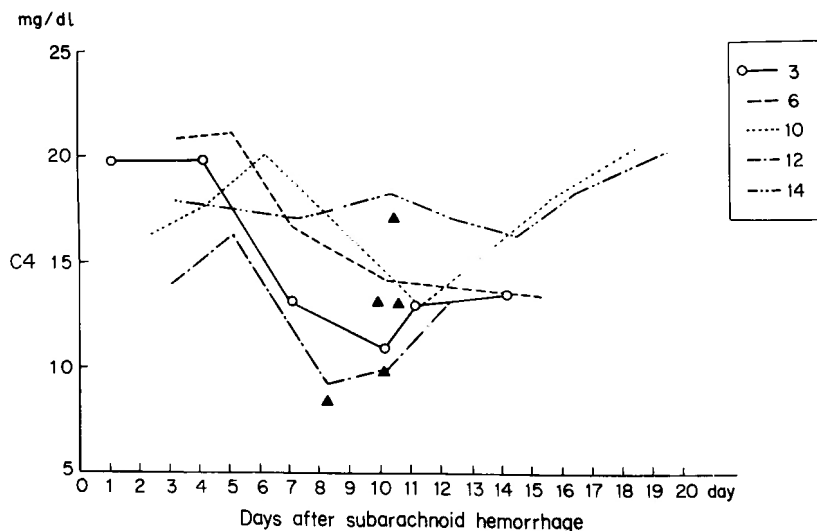


Fig. 4 Arrow heads show the time of recognized symptomatic vasospasm. Insets show case numbers. In every patient, decreases in serum C4 levels preceded onset of symptomatic vasospasm. One patient (case No. 8) who died 3 days after the operation was excluded.

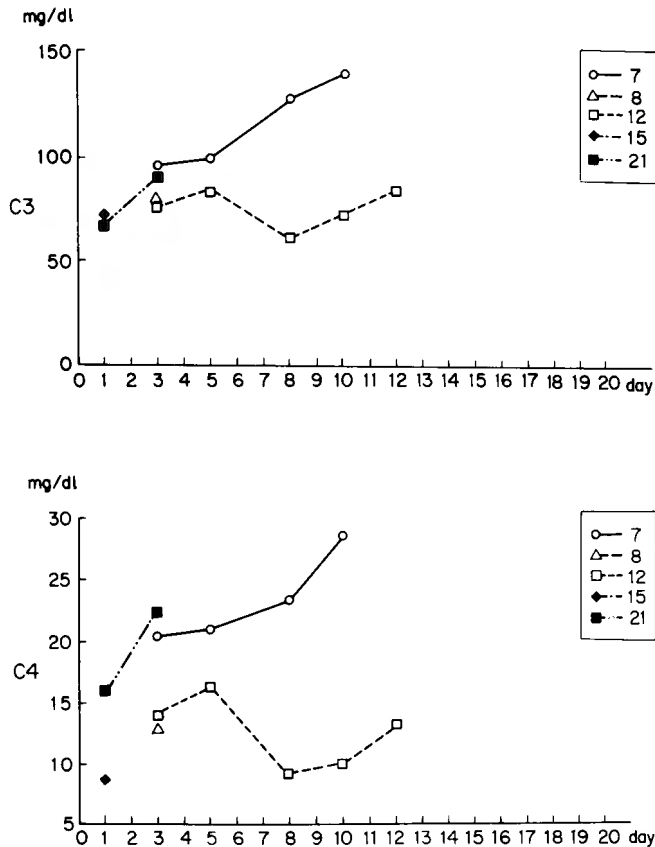


Fig. 5 Serum C3 (Upper) and C4 (Lower) levels in dead patients. There were no decreases of C3 and C4 levels in patients who did not die from delayed vasospasm.

II, 4 in grade III, 8 in grade IV and 3 in grade V. A summary of the cases appears in Table 1.

All of the cases were operated on within 72 hours after initial subarachnoid hemorrhage. In the postoperative management, mannitol, steroids and other anti-vasospasmotic agents could be used in every case. Not only cisternal irrigation and/or ventricular drainage were used in many cases, but induced hypertension and hypervolemic therapy¹⁰⁾ were used in cases that showed symptomatic vasospasm such as hemiparesis, aphasia and mental irritation.

Serum complements were assayed sequentially during a 2 to 3-week period after subarachnoid hemorrhage using the standard clinical examination method of *Mayer* for CH50, and by nephrometry for C3 and C4. For the control subjects, 4 patients who had intracerebral hematoma mainly caused by hypertension were chosen.

Statistical analysis was performed by using Students' *t* test and analysis of variance.

Results

1. Clinical analysis.

Five patients died during this study. Two out of 5 patients died from late cerebral vasospasm that originated from subarachnoid hemorrhage. We recognized symptomatic vasospasm in 6 pa-

tients (28.6%) during the investigation.

2. Sequential changes of serum complements in the control patients.

Figure 1 shows the sequential changes of serum complements (CH50, C3, C4) in the control patients. There are no statistical changes of C3 (Upper), CH50 (Middle) and C4 (Lower) levels after onset of the disease (by Analysis of variance).

3. Correlation between the initial grading and serum complements.

Figure 2 shows the correlation between the serum complements and the initial subarachnoid grading (Hunt and Hess). There was no correlation between the CH50 levels and the initial gradings, however, there was a weak correlation between the C3 levels and the initial gradings ($p < 0.05$). The greatest correlation was observed between the C4 levels and the initial gradings ($p < 0.01$). These results show that C4 level are the most useful indicators for predicting the severity of subarachnoid hemorrhage.

4. Sequential changes of C3 and C4 levels after subarachnoid hemorrhage.

Figure 3 shows the sequential changes of C3 and C4 levels after the subarachnoid hemorrhage.

These results show that C4 level are well correlated with symptomatic vasospasm. Furthermore, symptomatic vasospasm appears (arrow heads) after the C4 levels begin to decrease (Fig. 4).

Patients without symptomatic vasospasm showed progressive increases in C4 levels after subarachnoid hemorrhage in the range of over 20 mg/dl. On the other hands, C4 levels in patients with symptomatic vasospasm increased once just after onset, then decreased to below 20 mg/dl 3 to 5 days after onset of subarachnoid hemorrhage.

5. C3 and C4 levels in dead patients.

Figure 5 shows sequential changes of C3 and C4 levels in dead patients. Patients who did not die from late vasospasm showed no decreases in serum complements after subarachnoid hemorrhage, however, serum complements levels in patients who died from late vasospasm decreased suddenly when the vasospasm might have occurred after subarachnoid hemorrhage.

One patient (Case No. 12) who died from late cerebral vasospasm showed steep decreases of C4 levels 5 days after onset of subarachnoid hemorrhage. Other patients who showed mild symptomatic vasospasm without major neurological deficits showed more gradual decreases in C4 levels. Thus, C4 levels seems to decrease according to the severity of late cerebral vasospasm.

Discussion

In recent years, complement activation has been emphasized in many disease, especially those involving the vascular system such as systemic lupus erythematosus, glomerulonephritis, myocardial infarction, etc.^{1,3,4-6,11-15,21,22,24}. There are several reports on the cause of vasospasm after aneurysmal subarachnoid hemorrhage that state that complement activation is observed when the vasospasm occurs^{7,15,17,18}.

Pellettieri et al^{17,18} reported higher concentrations of circulating immune complexes in the blood in patients with subarachnoid hemorrhage and roentgenological and/or clinical vasospasm. *Hoshi et al*⁷ reported that patients who died from late cerebral vasospasm had immune complexes in their cerebral vessel walls. *Ostergaard et al*¹⁵ monitored circulating immune complexes and complement activation during a 2-week period in patients with ruptured cerebral aneurysms. They stressed circulating immune complexes as a cause of late cerebral vasospasm.

Although several reports have been published on this topic, no ideal biochemical marker for

predicting late cerebral vasospasm have been identified. Angiography is the best method for detecting cerebral vasospasm, however, the contrast medium as well as angiography itself can worsen vasospasm. Since measuring circulating immune complexes is somewhat difficult, we measured serum complements instead as indicators of late cerebral vasospasm and the severity of the vasospasm.

Complement activation reflects a decrease of C3 and C4 levels. Among serum complements, C4 seems to be the most reliable biochemical marker for predicting late cerebral vasospasm. Sequential change of C4 levels are well correlated with the occurrence and severity of vasospasm. Measuring serum complements is now quick and easy in most clinical laboratories. We can now assume that patients with decreasing C4 levels after 3 to 5 days will have an increased chance of developing symptomatic vasospasm. This also make it possible to chose method of therapy for neurological deterioration in aneurysmal patients, such as induced hypertension, hypervolemia, and the use of anti-vasospasmodic agents.

It is well known that complement activation occurs via either the classical pathway or alternative pathways. Since we could not measure serum C1 levels, we can not confirm that complement activation after subarachnoid hemorrhage occurred via either pathway. In this study, C4 levels were well correlated with late cerebral vasospasm, possibly via classical pathway.

When the classical pathway is involved in late cerebral vasospasm, it is reasonable to prescribe a C1 inhibitor. On the other hand, when the alternative pathway is involved, plasma exchange could be useful because it removes circulating immune complexes after subarachnoid hemorrhage.

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和文抄録

破裂脳動脈瘤によるクモ膜下出血後の脳血管攣縮の重症度と予後推定因子としての血清補体測定の有用性について

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破裂脳動脈瘤患者の予後を決定づけるものは、クモ膜下出血後の重症度と共に遅発性の脳血管攣縮の発生の有無による。脳動脈瘤の術前術後の管理の進歩により、重症脳動脈瘤患者の救命率も向上しつつあるが、遅発性脳血管攣縮については根本的治療法がなく、依然として神経学的脱落症状を残す症例があり、更には致命的にもなっている。本研究では、脳血管攣縮の発生病因を炎症説として捉え、クモ膜下出血後の血清中の補体価(CH50)、補体(C3, C4)を測定し、脳血管攣縮との関連性を検討した。対象とした患者は何れも急性期手術がなされた21人の破裂脳動脈瘤患者である。コントロールとしてはクモ膜下出血を主体としない、4例の脳内出血患者を選んだ。コントロールでは発症後2週間にわたり、補体価、補体

とも有為な変動は認められなかった。破裂後急性期の重症度とCH50とは相関は認められず、C3と弱い相関があり、C4とは最も相関が認められた。症候性血管攣縮との関連性については、症候性攣縮をきたし神経学的脱落症状を残した患者ではC4の低下が発症後5-10日めに認められ、低下の度合いが強かったが、症候性血管攣縮をきたし神経学的脱落症状を残さなかったものではC4は発症後一過性に低下したがその後の回復が良好であった。これに対して、症候性攣縮をきたさなかったものではC4の低下は認められなかった。以上の事は、血清中の補体の測定を行なうことにより、血管攣縮の重症度がより客観的に捉えられ、ひいては脳血管攣縮発生の際の治療法の選択をも可能にしてくれることを示唆している。